STARTING, SWITCHING OR STOPPING NEW ORAL ANTICOAGULANTS: A Practical Approach

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Disclosure

Grants/Research Support: CIHR, HSFO, CFI, ORF

Consultant: Bristol-Myers Squibb, Boehringer Ingelheim, Sanofi-Aventis, Daiichi-Sankyo, Bayer, Pfizer, Johnson and Johnson
Overview

New oral anticoagulants

Management issues
• Starting
• Switching
• Monitoring
• Stopping
Dabigatran and rivaroxaban licensed for stroke prevention in atrial fibrillation

Rivaroxaban licensed for treatment of DVT

Dabigatran, rivaroxaban and apixaban licensed for thromboprophylaxis after hip or knee replacement surgery
New Oral Anticoagulants

Thrombin
  - Dabigatran

Factor Xa
  - Rivaroxaban
  - Apixaban
  - Edoxaban
## Advantages of New Oral Anticoagulants Over Warfarin

<table>
<thead>
<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>New Orals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Offset</td>
<td>Long</td>
<td>Shorter</td>
</tr>
</tbody>
</table>
### Disadvantages of New Oral Anticoagulants Over Warfarin

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>New Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>Once daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Monitoring</td>
<td>INR</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Clearance</td>
<td>Non-renal</td>
<td>Renal 25-80%</td>
</tr>
<tr>
<td>Antidote</td>
<td>Vit K, FFP, PCC</td>
<td>None</td>
</tr>
<tr>
<td>Familiarity</td>
<td>Extensive</td>
<td>Limited</td>
</tr>
</tbody>
</table>
## Comparative Pharmacology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>80%</td>
<td>60%</td>
<td>6%</td>
</tr>
<tr>
<td>Dosing</td>
<td>o.d. (b.i.d.)</td>
<td>b.i.d.</td>
<td>b.i.d. (o.d.)</td>
</tr>
<tr>
<td>Half life</td>
<td>7-11 h</td>
<td>12 h</td>
<td>12-17 h</td>
</tr>
<tr>
<td>Renal</td>
<td>33% (66%)</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td>Monitoring</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>3A4/P-gp</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>
Who Is Not a Candidate For New Oral Anticoagulants?

- Stable on warfarin?
- CrCl less than 30 ml/min
- Severe hepatic dysfunction
- Mechanical valve
- Non-compliant with warfarin
Management Issues With New Oral Anticoagulants

- Starting
- Switching
- Monitoring
- Stopping
Starting New Oral Anticoagulants

Rapid onset of action with peak plasma concentrations in 1 to 3 h

No need for bridging
Switching from Warfarin to New Oral Anticoagulants

Peak onset of action of new agents occurs within 2 to 3 hours

Initiate when INR is 2.0 or lower; 2.5 or lower in high-risk patients
Switching from Dabigatran to Warfarin

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Days prior to dabigatran discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>- 3</td>
</tr>
<tr>
<td>31 – 50</td>
<td>- 2</td>
</tr>
<tr>
<td>15 – 30</td>
<td>- 1</td>
</tr>
</tbody>
</table>
Switching from Rivaroxaban to Warfarin

Overlap warfarin with rivaroxaban; determine INR at rivaroxaban trough on day 2 and stop rivaroxaban when INR is $\geq 2.0$
Switching from Dabigatran or Rivaroxaban to Heparin or LMWH

Stop dabigatran or rivaroxaban and start heparin or LMWH 12 or 24 h later, respectively
Monitoring
Why Monitor?

Assess adherence
Confirm dosing adequacy
Detect accumulation / overdose
Plan timing of urgent surgery
Identification of bleeding mechanism
Patient reassurance
A 78-year-old man with atrial fibrillation, hypertension, and type II diabetes mellitus is on dabigatran 150 mg bid. He presents with an acute ischemic stroke in the left MCA distribution with no evidence of bleeding on the CT scan. Symptoms started 2 hours ago. You are considering tPA. What test would be best to assess the safety of this approach?

1. Prothrombin time (INR)
2. Activated partial thromboplastin time
3. Thrombin time
4. Hemoclot time
5. Anti-IIa assay
Dabigatran Monitoring

aPTT

Hemoclot Test

Rivaroxaban Monitoring

PT

Rotachrom Anti-Xa

New Oral Anticoagulants and Routine Tests of Coagulation

Dabigatran prolongs the aPTT more than the PT, whereas rivaroxaban has a greater effect on the PT

Rivaroxaban prolongs the PT more than apixaban

At high concentrations, all of the agents prolong the PT and aPTT
Potential Strategies

• Crude assessment of adherence or offset
  – Dabigatran: aPTT
  – Factor Xa inhibitors: PT

• Monitoring of blood levels
  – Dabigatran: Hemoclot test
  – Factor Xa inhibitors: anti-Xa assay (e.g., Rotachrom)
Stopping
Peri-procedural Anticoagulant Management

Determine bleeding risk of planned procedure

If bleeding risk is low (e.g., dental cleaning/extractions, cataract surgery, skin biopsy), no need to stop anticoagulant
Peri-procedural Anticoagulant Management

If bleeding risk is moderate to high:

• stop anticoagulant

• determine creatinine clearance
## Timing of Discontinuation of Dabigatran Prior to Procedures

<table>
<thead>
<tr>
<th>Renal function (CrCl ml/min)</th>
<th>Half-life, hours (range)</th>
<th>Discontinuation of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Moderate bleeding risk</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>15 (12 – 34)</td>
<td>1 - 2 days</td>
</tr>
<tr>
<td>31 - 50</td>
<td>18 (13 – 23)</td>
<td>3 – 4 days</td>
</tr>
<tr>
<td>≤ 30*</td>
<td>27 (22 – 35)</td>
<td>4 – 5 days</td>
</tr>
</tbody>
</table>

*Dabigatran is contraindicated for use in patients with severe renal impairment (CrCl < 30ml/min)

Adapted from:
2. Pradax Monograph 2010, Boehringer Ingelheim Canada Ltd
<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>31-50</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>≤ 30</td>
<td>2 days</td>
<td>3 days</td>
</tr>
</tbody>
</table>
Conclusions

Selection of appropriate patients for new oral anticoagulants is essential

An understanding of the pharmacology of the new agents enables optimal approaches to their starting, switching, monitoring, or stopping